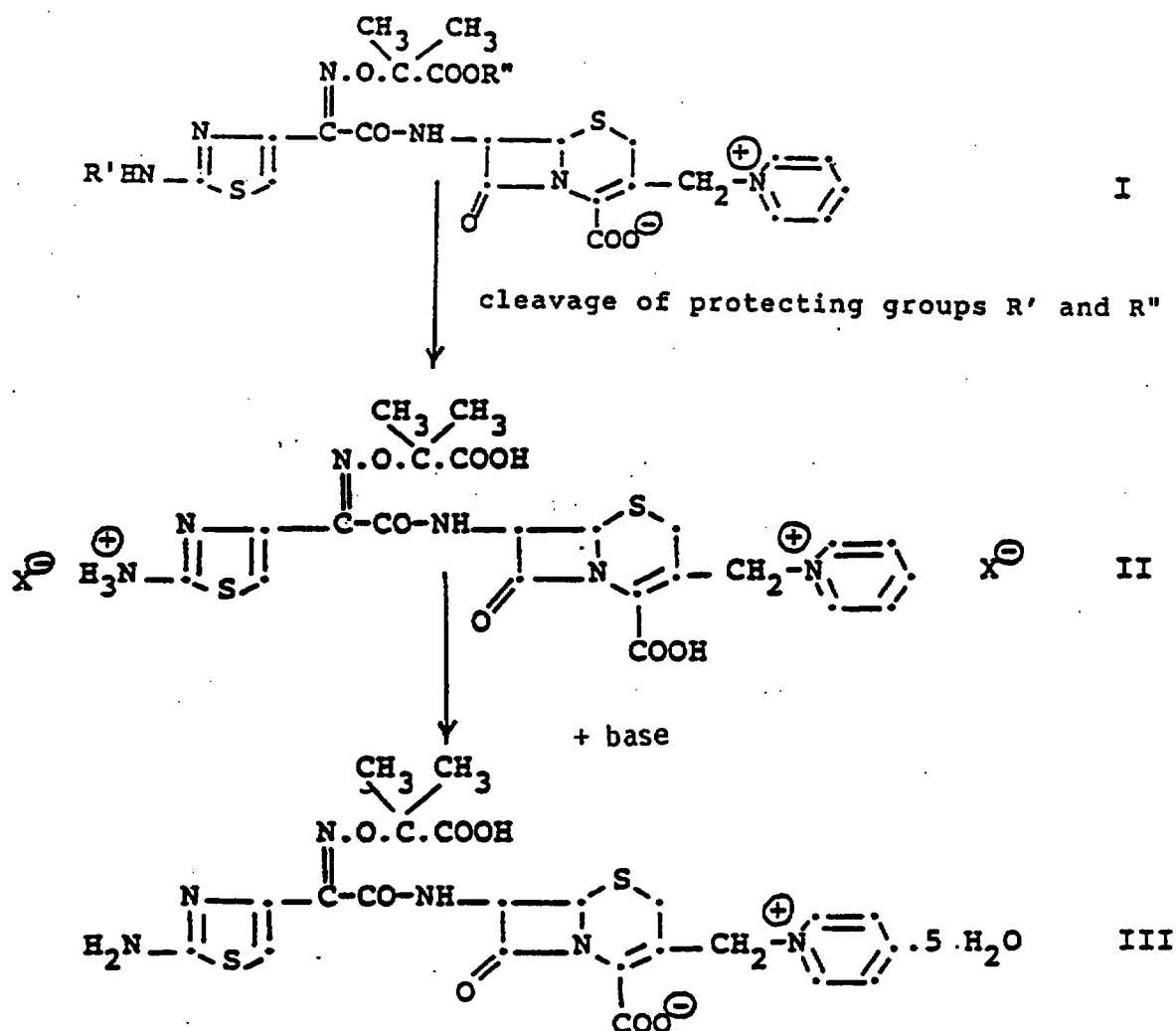


### Process for the preparation of cephalosporin derivatives

The invention relates to an improved, simplified and new process for the preparation of the antibiotic ceftazidime pentahydrate.

Ceftazidime is a valuable antibiotic. The production thereof is described, among other things, in GB Patent Specification 2025 398. Ceftazidime may be obtained in various forms, as the dihydrochloride, dihydrobromide or as the pentahydrate. The pentahydrate is the preferred form and is described for example in GB Patent Specification 2063 871. The known processes, which lead to this preferred form of the pentahydrate, follow the course drafted in the following formula scheme:



In the processes for the preparation of ceftazidime pentahydrate (formula III) which are known from literature, at first the compounds of formula II, which represent ceftazidime as the dihydrohalide, are prepared and isolated from compounds of formula I, which represent the mono- ( $R' = \text{hydrogen}$ ) or di-protected ( $R' = \text{protecting group}$ ) ceftazidime (GB 2063871) or purification of the ceftazidime from the cleavage products is attained by extraction processes (EPA 179546), before the ceftazidime may be isolated as the pentahydrate. This intermediate isolation of the dihalide or the purification of the solution containing ceftazidime after cleavage of the protecting groups is necessary, since the cleavage products arising from the cleavage of the protecting groups prevent crystallisation of the pure pentahydrate, or at least make it extremely difficult. In addition, because of the use of considerable amounts of organic acids for the cleavage of the protecting groups (usually formic acid), when the ceftazidime is directly isolated as the pentahydrate without intermediate isolation of the ceftazidime as the dihydrohalide, a considerable salt loading would be given upon precipitation of the pentahydrate, which takes place at a pH value of about 3.6 to 4, which again to a great extent prevents crystallisation of the ceftazidime as the pentahydrate.

In accordance with the invention, it has now surprisingly been found, that it is possible to crystallise the pentahydrate of the ceftazidime directly starting from the compound of formula I, wherein  $R' = \text{H}$  and  $R'' = \text{t-butyl}$ , without having to go through the isolated intermediate of a dihalide. The process according to the invention is characterised in that only hydrochloric acid is used for the cleavage of the protecting group  $R'' = \text{t-butyl}$ .

Whilst in the known processes, beside the use of hydrochloric acid, always further (organic) acids, which usually also serve as

solvents, are used, such as formic acid, dichloroacetic acid, trifluoroacetic acid or trichloroacetic acid, the process according to the invention is limited to the sole use of hydrochloric acid. Due to the omission of the other (usually organic) acids, a considerable advantage is obtained so far as when there is direct processing to the pentahydrate, which is isolated at about pH 3.6 to 4, only the hydrochloric acid employed must be neutralised, while in the case of the additional use (or even sole use) of an organic acid in a large excess, as is usual in conventional processes, a vast amount of salt is produced in the direct neutralisation, which makes crystallisation of the pentahydrate of ceftazidime very difficult.

A further advantage of the process according to the invention is the high concentration at which the process is carried out, whereby large quantities of product may be produced within short time and with a small reactor volume. A further advantage of the process according to the invention is that, apart from hydrochloric acid (and a base for neutralisation), no chemicals or solvents are required, which represents a considerable financial and ecological advantage.

However, apart from all these advantages of the process according to the invention, there is also the possibility of isolating the intermediate of the dihydrochloride of ceftazidime (formula II; X = chloride), whereby this also gives the advantages regarding ecology and easy recovery of the solvents. It is known from EPA 157538 to induce crystallisation of ceftazidime dihydrobromide directly from the reaction mixture after the reaction of the di-protected ceftazidime ( $R'$  = protecting group) with formic acid/hydrobromic acid by adding a water miscible solvent.

When isolating the compound of formula II in the process according to the invention, a further advantage becomes clear, since as a result of the sole use of hydrochloric acid for the ester cleavage, the compound of formula II can be obtained particularly easily and in highly pure form. In contrast to known processes - in which the reaction mixture is usually quenched with huge amounts of acetone - the process according to the invention allows a simple and slow crystallisation of the dihydrochloride of ceftazidime by simple addition of solvents such as acetone and/or ethanol to the reaction mixture, whereupon the dihydrochloride of ceftazidime is obtained in highly pure form in readily isolable crystals. The dihydrochloride isolated in this way is characterized by its good purity (HPLC  $\geq$  93%), which leads to considerable advantages in the conversion into the pentahydrate of ceftazidime (increased crystallisation yields).

When isolating the dihydrochloride, the mother liquor may be recovered or disposed of in a simple way, since it does not contain any solvents beside acetone and hydrochloric acid and small quantities of iso-butene. For this, it is sufficient to neutralise the mother liquor using (optionally solid) alkali lye (to avoid corrosion in distillation) and to distill off or rectify the acetone. The acetone thus obtained may then be used again to precipitate the compound of formula II.

The process according to the invention, which instead of the otherwise usual organic acids or mixtures of organic acids with a hydrohalic acid, is limited to the sole use of aqueous hydrochloric acid for cleavage of compounds of formula I, thus allows both the preparation of the compound of formula II (X=chloride) which is regarded as an intermediate, as well as the direct preparation of the pentahydrate of ceftazidime (formula III) in highly pure form ( $\geq$  97% on an anhydrous basis) and in an excellent yield (70% and higher) in a simple manner.

In the process according to the invention, the t-butylester of ceftazidime may be employed in any crystal form or also as an acid addition salt.

The following examples illustrate the invention more fully, but in no way limit it. All temperatures are given in degrees centigrade. The water evaluations were made by the Karl-Fischer method.

Example 1: Ceftazidime pentahydrate

65 g of ceftazidime-t-butylester (crystalline in  $\beta$ -form) are added at 0 to 5° to 80 ml of conc. HCl (11 normal), whereby a light yellow solution results. This is stirred further for 1 hour at 5°, until ester cleavage is complete (control by thin-layer chromatography or HPLC). Then, 80 ml of ice water are added to the solution, and upon good cooling the pH value is adjusted to 4.1 with 5 N NaOH at a max. of +5°. It is left to stand for 1 hour at 5 to 10°, whereby the product begins to crystallise out. Then, the pH value is adjusted to 3.8 with 3 N HCl, and after a further one hour to pH 3.6, whereby the temperature is always kept at between +5 and +10°. Finally, cooling is effected to 0 to 4° for 5 hours. The precipitated crystals are then filtered off, washed with cold water and acetone, and dried at room temperature. 46.5 g of the title compound are obtained (73% of theory) in the form of a white crystalline powder.

Content (HPLC; on H<sub>2</sub>O-free basis): 97.0%

Water content (Karl-Fischer): 14.5%

Example 2: Ceftazidime pentahydrate

70.2 g of ceftazidime-t-butylester (crystalline in  $\alpha$ -form) are added at 0 to 5° to 100 ml of conc. HCl, whereby a light yellow-greenish solution results. This is stirred further for 1 hour at 5°. Then, 120 ml of ice water are added, followed by solid sodium bicarbonate, until a pH value of 4.0 - 4.1 has been attained. The temperature is thereby kept at below +5°. It is then left to stand for 1 to 2 hour at about 10 to 15°, whereby the product begins to crystallise out. Then the pH value is adjusted to 3.6 with 3 N HCl, and left to stand for another 5 hours at 0 to 4°. The title compound is then isolated, washed with cold water and acetone, and dried. In this way, 44.3 g (70%) of the title compound are obtained in pure form (HPLC content:

97.3%, H<sub>2</sub>O content: 14.6%).

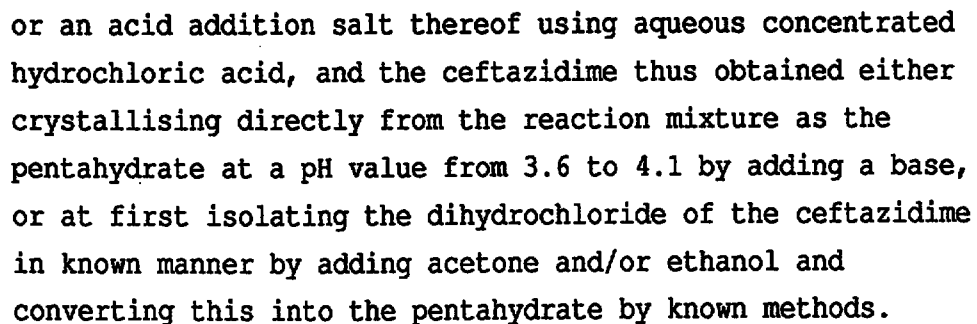
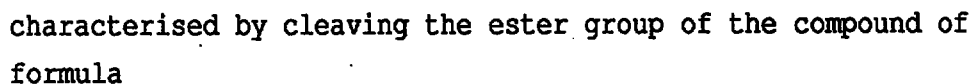
**Example 3: Ceftazidime dihydrochloride**

130 g of ceftazidime-t-butylester (crystalline in  $\beta$ -form) are added at 10° to 150 ml of conc. HCl, whereby a yellow solution results. This is stirred further for one hour at 10°. Then 300 ml of acetone are added and allowed to crystallise for 30 minutes. The product separates in the form of fine regular crystals. To complete crystallisation, a further 700 ml of acetone are added over a period of 90 minutes, and stirring is effected further for one hour. The crystals are subsequently isolated, washed with acetone and vacuum-dried. 120 g (97%) of the title compound are obtained in the form of white free-flowing crystals with a content of 94% (HPLC).

**Example 4: Ceftazidime pentahydrate**

60 g of the ceftazidime dihydrochloride obtained as described in Example 3 are dissolved in 300 ml of ice water. The acidic solution (pH 0.7-0.8) is clear-filtered to remove solid particles and the pH is then adjusted to 4.0 with about 160 ml of 3 N NaOH at a maximum of 10°. After crystallisation for 2 hours, the pH is adjusted to 3.6 and left for crystallisation for further 3 hours at about 5°. The product is then filtered off by suction, washed with cold water and acetone and dried. 50 g (87%) of the title compound are obtained in the form of colourless crystals with a content of  $\geq 97\%$ .

1) New process for the preparation of the pentahydrate of ceftazidime of formula





- 2) Process according to claim 1, characterised in that the concentration of the aqueous hydrochloric acid is 20 to 40% by weight.
- 3) Process according to claims 1 and 2, characterised in that the ester cleavage is carried out at -15 to +35°C.
- 4) Process according to claims 1 to 3, characterised in that the pentahydrate of ceftazidime is crystallised from the reaction solution directly without intermediate isolation of the ceftazidime dihydrochloride.
- 5) Process according to claims 1 to 3, characterised in that the dihydrochloride of ceftazidime is crystallised from the reaction mixture by adding acetone and/or ethanol, and this is converted into the ceftazidime pentahydrate by known methods.
- 6) Process for the preparation of the dihydrochloride of ceftazidime, characterised in that the ester group of the compound of formula Ia, as illustrated in claim 1, or an acid addition salt thereof, is cleaved using aqueous hydrochloric acid, and the so obtained dihydrochloride is crystallised in known manner by adding acetone and/or ethanol.